AREA OF EMPHASIS:

International Research

SCIENTIFIC ISSUES

Now in its third decade, the AIDS epidemic continues its relentless spread across the globe. The devastating effects of the AIDS pandemic are broad, wiping out development gains, decreasing life expectancy, increasing child mortality, orphaning millions, setting back the situation of women and children, and threatening to undermine national security in highly affected societies. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) report entitled *AIDS Epidemic Update*, at the end of 2004:

- An estimated 39.4 million people worldwide were living with HIV/AIDS;
- Approximately 2.2 million were children under the age of 15 years;
- About half of the infected adults were women;
- An estimated 4.9 million people (adults and children) acquired HIV in 2004; and
- The global HIV/AIDS epidemic killed more than 3.1 million people in 2004.

UNAIDS notes in its report that the sub-Saharan Africa region remains by far the hardest impacted region with an estimated 25.4 million people living with HIV/AIDS and approximately 3.1 million new infections during 2004. After sub-Saharan Africa, the Caribbean is the most affected region in the world, with an overall prevalence rate of approximately 2.3 percent among adults. Between 2002 and 2004, the number of people living with HIV has risen in every region of the world, with the steepest rise recorded in East Asia (50 percent) and in Eastern Europe and Central Asia (40 percent). An increasing proportion of people living with HIV are

women and girls (15–49 years of age), and that proportion is continuing to grow, particularly in Eastern Europe, Asia, and Latin America.

Research is an essential component of a comprehensive approach to address the AIDS pandemic. Since the early days of the epidemic, the NIH has supported an increasing research effort in countries affected by HIV and AIDS. Beginning in 1984 with a research project in Haiti and the establishment of Projet SIDA in 1985 in what was then Zaire, the NIH has maintained a strong international research portfolio.

The NIH international research portfolio continues to evolve in order to develop and test effective and safe interventions for the prevention and treatment of HIV/AIDS in resource-constrained countries. Since 2000, when the Office of AIDS Research (OAR) established a new initiative and plan for global research on HIV/AIDS, the plan has been subject to annual revisions in order to identify the highest priorities for the conduct of research in international settings.

There is great diversity among international settings with respect to prevention and treatment research needs. An overriding principle guiding the conduct of NIH-supported international AIDS research is that the research effort must be relevant to the cultural, social, and economic context of the country where the research is conducted. To accomplish this goal, NIH-supported research programs strive to involve the local community throughout the development, conduct, and analyses of the research and ensure a leadership role for in-country scientists.

PRIORITY FOR FUTURE RESEARCH:

- **Develop in-country HIV/AIDS research training and research infrastructure.**

Various sections of the NIH Plan for HIV-Related Research describe research efforts to develop HIV vaccines; chemical and physical barrier methods, such as microbicides, to prevent sexual transmission; behavioral strategies targeted to the individual, family, and community to alter risk behaviors associated with sexual activity and drug and alcohol use; drug and nondrug strategies to prevent mother-to-child transmission (MTCT); therapeutics for HIV-related coinfections and other conditions; and antiretroviral therapy (ART) regimens and strategies for widespread use. Before prevention and treatment interventions can be implemented in resource-poor nations, their safety and efficacy must be demonstrated in these settings by clinical trials and other intervention research. However, in many resource-poor countries, adequate research training and infrastructure may not exist to conduct such trials and must be developed.

The development of research infrastructure through training in-country scientists, clinicians, and other health care workers; strengthening laboratory and clinical capacity; and enhancing research collaborations will help to address many of the

existing challenges to the conduct of research in resource-limited settings. Ethical considerations must be paramount in the development of international collaborations and NIH-supported research activities in other countries. It is universally accepted that researchers should adhere to the highest ethical and scientific principles in the design and conduct of research. Essential to the protection of human subjects participating in research, these principles are outlined in several documents and include respect for persons, beneficence, and justice.

The vastly different economic and cultural contexts in which research is conducted in international settings create many challenges for researchers and funding agencies. For example, obtaining voluntary informed consent from each study participant may be complicated in some settings by social customs requiring the involvement of others in the community in this process, such as family members or community leaders. In addition, lengthy and complex informed consent forms used in the United States may be problematic to use in these settings. Differences in laws, regulations, and public policy, as well as organizational structures, mean that careful consideration must be given to how ethical standards of both the United States and the country where research is conducted can be met. To this end, a constant and consistent dialogue is needed among U.S. and foreign investigators, foreign institutional review boards (IRBs), staff of the DHHS Office for Human Research Protections, NIH program managers, and ethicists.

Similarly, compliance with regulatory requirements in resource-poor settings often poses serious challenges that may result in long delays and added costs to key research studies. In addition, just as there is a significant difference between clinical hospital sites in the United States and developing countries, there also is a difference between developing country hospitals and field sites in their capacity to implement regulatory requirements. In this regard, it is important to indicate early in the research planning process whether or not the research is intended to support product approval by the U.S. Food and Drug Administration (FDA). Dialogue similar to that for ethical considerations is needed to develop a common understanding of regulatory requirements and should include U.S. and foreign investigators, FDA staff, NIH program managers, and industry representatives as appropriate.

Several principles guide the development of infrastructure. One is that many of the clinical and infrastructure needs for clinical trials are best developed through the conduct of research in these settings, since population-based research is an effective means to prepare for eventual clinical trials. A second principle is that infrastructure development is enhanced when the research effort is integrated with ongoing health care and prevention services and when prevention and care services themselves are integrated, enabling prevention messages to be delivered in the care setting.

Specific infrastructure needs are many. In order to move quickly with clinical trials of promising candidates and strategies, research sites must be strengthened

through establishment of stable, targeted cohorts; development of recruitment and retention strategies; and enhancement of laboratory, clinical, and data management capabilities. To ensure the leadership role of in-country researchers, it is critical to increase the number of scientists, clinicians, and health care workers of all levels and disciplines who are trained in basic, clinical, and behavioral research; data management; program management and administration; and ethical considerations. To develop an adequate cadre of researchers in resource-limited countries, it is also essential to develop strategies to retain researchers in-country and enhance the careers of trained personnel. There also is the need to develop strong and effective research collaborations involving both U.S. and international colleagues. Finally, high-quality research in resource-limited settings can be carried out only if adequate clinical and laboratory technologies are transferred to such settings. In order to adequately strengthen infrastructure, it is critical to devise innovative funding mechanisms and approaches, such as the evolving policy on the provision of indirect costs to foreign institutions.

PRIORITY FOR FUTURE RESEARCH:

- **Conduct research to identify a comprehensive set of effective, appropriate, and sustainable interventions to curtail HIV transmission, including a combination of approaches at multiple levels to target existing and emerging at-risk populations.**

The NIH is pursuing international research in all scientific areas that address HIV transmission. From a global perspective, the major modes of acquiring HIV infection are unprotected heterosexual intercourse and injecting drug use, with the vast majority of infections occurring through sexual transmission. Appropriate and acceptable biomedical and behavioral interventions to curb this transmission in very diverse settings are urgently needed, including interventions that address specific populations at high risk, such as women and adolescents.

Behavioral and social interventions are needed at all levels: individual, family, social network, community, and society. These interventions must be developed for HIV-seropositive, as well as HIV-seronegative individuals. Women are particularly vulnerable; therefore, it is critical to develop microbicides and other prevention methods that can be controlled by women. It is important to address social factors that contribute to vulnerability to HIV transmission and that serve as possible points of intervention. These include poverty, limited access to health care, stigma and discrimination, and gender inequality. Research also is needed to devise strategies to decrease HIV transmission in health care settings.

Two prevention interventions merit special attention: prevention of MTCT and transmission related to drug and alcohol use. While clinical trials have demonstrated that a variety of short, simple, effective, and inexpensive antiretroviral (ARV)

regimens can reduce MTCT by up to 50 percent, the results have been slow to be implemented, and postnatal transmission through breastfeeding remains a significant problem. New interventions will need to be developed to further reduce MTCT, and operations research will need to be conducted to facilitate implementation of effective prevention strategies and regimens.

Injecting drug use is an increasingly important factor in the AIDS epidemic. As a social phenomenon, injecting drug use itself is reported to be increasing in all regions of the world, including Africa. Thus, the potential exists for drug-related epidemics to arise in new places and for escalation of established epidemics. In some countries in Asia and Central and Eastern Europe, injecting drug use is the major route of HIV transmission. Recent rapid increases in HIV infections in China, Indonesia, and Viet Nam show how an epidemic can erupt suddenly whenever significant levels of injecting drug use occur. Injecting drug users (IDUs) are particularly vulnerable to HIV infection because they are often poor and marginalized.

The use of noninjecting drugs, including alcohol, is associated with increased risk, particularly through associated sexual behavior. In many parts of the world, drug use and sexual transmission of disease are inextricably linked, and drug users are more likely to be involved in the sex industry, greatly enhancing their risk of infection and the chance that HIV will spread even wider in the community. Culturally relevant interventions are needed to prevent transmission related to drug and alcohol use. To ensure that newly developed interventions are culturally appropriate, it is critical to conduct research that investigates the social context of drug and alcohol use and to involve the community at all levels of the research.

PRIORITY FOR FUTURE RESEARCH:

- **Conduct both experimental and observational research to identify appropriate care and treatment strategies to limit the impact of HIV-related disease.**

The use of ART has extended the length and improved the quality of life for many HIV-infected people in industrialized countries. These therapies are only now beginning to be utilized in several resource-poor nations, due to factors such as cost and the need for an adequate health care infrastructure to administer and monitor these therapeutic regimens. Treatment programs have been launched by international organizations (e.g., the World Health Organization [WHO], the Global Fund to Fight AIDS, Tuberculosis and Malaria [GFATM]), U.S. initiatives and organizations (e.g., the President's Emergency Plan for AIDS Relief [PEPFAR]), and a large number of nongovernment organizations (NGOs). It is, therefore, critical to move rapidly to investigate the safety and efficacy of various ART regimens for both adults and children in diverse resource-poor settings. For example, differences in diet, nutritional status, or the use of medications for endemic diseases may alter

the toxicity or the efficacy of ARVs as compared with industrialized areas. Practices in industrialized countries may not be directly applicable, due to many factors such as existing health care infrastructure, social structure, and the presence of other endemic diseases, as well as factors related to the patients themselves and their families. Thus, many questions about how to treat and how to monitor HIV-infected patients must be adapted to variable developing country settings. Research is needed to address adherence to medication regimens in these settings and ways to monitor and improve it. Any ART program will be associated with variable levels of drug resistance to one or more ARVs, an issue that will require different types of research studies, ranging from basic science laboratory investigations to studies of ART effectiveness and outcome research, in order to document its mechanistic underpinnings, its epidemiologic features, and its possible consequences at the individual and population level. Studies also will be warranted regarding the potential increase of high-risk behaviors that, as a result of a false sense of security, may occur when ART becomes more widely available.

Research on treatment strategies and specific regimens will be necessary to understand and curtail possible undesired effects of therapies. In the industrialized world, extended survival in individuals receiving ART has been associated with the development of a spectrum of new systemic conditions, e.g., metabolic and cardiovascular disorders. As the use of ART increases in the developing world, it will be necessary to characterize new pathologic conditions that may be influenced by factors such as diet, the presence of endemic diseases, and the use of drugs to treat them.

Operational research questions must be addressed about the implementation of current technologies for viral load and CD4+ cell measurements and the development of lower cost methods and alternatives for these tests. Finally, a dialogue with the pharmaceutical industry should be continued concerning the provision of drugs for the research effort and for treatment regimens once they have been demonstrated safe and efficacious. The new NIH *Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries* recommends that investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of ART after completion of the study.

Since the beginning of the AIDS epidemic, research has been conducted in the industrialized world to characterize the opportunistic infections (OIs) that affect individuals whose immune systems are weakened by HIV. Methods for diagnosis, prevention, and treatment of OIs have been developed. The extensive use of potent ART in the industrialized world has resulted in a dramatic decrease in many of these infections and their related morbidity and mortality. In the developing world, however, OIs associated with HIV infection continue to result in high morbidity and mortality. Much remains to be elucidated about the extent of endemic coinfections, cancers, neurologic manifestations, and other conditions associated

with HIV infection in these settings. It is necessary to develop and assess different and complementary modalities to prevent and treat them, particularly since ARVs are only beginning to be used in these settings. The needs of both adults and children must be addressed in these efforts. As a foundation for the development of such interventions, it is essential to characterize the nature, prevalence, risk factors, and disease course of endemic coinfections, as well as other HIV-related conditions found in diverse geographic settings. An integral component of this effort is the development of diagnostic methods to detect these illnesses.

Important new information about the global extent and nature of concomitant infection with hepatitis C virus (HCV) is beginning to emerge, and research is needed to further characterize HIV/HCV coinfection. The HIV-related global epidemic of tuberculosis (TB) is well documented, with approximately a third of the world's population of HIV-infected individuals coinfected with *Mycobacterium tuberculosis*. As TB is now the leading cause of death among HIV-infected individuals worldwide, research to develop approaches for the prophylaxis and treatment of TB remains a priority.

Further, little is known about other infections and resulting pathologic conditions. Some are closely related to specific environments. For example, fungal infections might prevail in one setting and bacterial infections in another. Diseases not found in industrialized nations may be important in more resource-diverse regions (e.g., a fungal infection due to *Penicillium marneffei* is an important coinfection in HIV-infected individuals in some areas of Southeast Asia, where the agent is endemic). In addition, it will be critical to examine the impact of new interventions on diseases such as malaria, not previously thought to be related to HIV disease but a major cause of morbidity and mortality in developing countries.

PRIORITY FOR FUTURE RESEARCH:

- **Conduct research to examine the interactions among aspects of treatment and prevention, including the impact of therapy on the HIV epidemic.**

There is an urgent need in resource-poor countries for effective, culturally appropriate, and sustainable interventions to prevent transmission of HIV and to treat HIV infection and its associated complications in both adults and children. Integration of prevention and care interventions will ensure that an increasing proportion of the population has access to all necessary health services. This integration concept recognizes that prevention, care, and treatment are closely interrelated. Treatment interventions will not succeed if prevention strategies are failing, as there will be more people requiring treatment. Prevention interventions alone will not succeed if treatments are not accessible. NIH-sponsored research can identify and test such interventions.

Institutional challenges include the need to link research programs with prevention, treatment, and care programs, integrating prevention and care where warranted; enhancing the ability of study sections and review groups to address proposals for international research; and developing the expertise of NIH program and grants management staff to manage international research portfolios. In addressing all of these institutional issues, coordination among funding agencies—within the United States and around the world—will be necessary. The establishment of a database that tracks ongoing efforts funded through a variety of mechanisms would be of valuable assistance in such coordination. In addition, a single, comprehensive source of information relevant to the conduct of research, such as application procedures, ethical and regulatory requirements, and other policy issues would be of great assistance to foreign investigators and their U.S. collaborators.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE – A:

Develop a sustainable research environment by harnessing existing and further enhancing in-country capacity, including expanding research training opportunities, addressing ethical issues, meeting Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) requirements, and enhancing computer/Internet capability and connectivity for improved communication, access to information resources, data management, and statistical analysis.

STRATEGIES:

Site Development

- Encourage the integration of NIH-supported research programs being conducted in resource-limited countries by U.S. researchers with established in-country programs, including collaboration with local investigators on strategic planning for research.
- Assess existing sites and, as needed, further develop sustainable, existing in-country sites, or establish new international research sites as rapidly as possible to address urgent and emerging scientific opportunities.
- Enhance capacity for the conduct of basic and applied prevention and treatment research, with emphasis on GCP requirements for large-scale clinical trials through:
  - strengthening laboratory capacity with appropriate quality assurance and training;
  - developing clinical capabilities to enable the conduct of research;
  - developing affordable alternatives to viral load and CD4+ cell counts and expensive laboratory monitoring for treatment efficacy and toxicity;
  - supporting the analysis of scientific and research-based international databases and developing common laboratory information management systems;
  - enhancing data collection and analysis capabilities;
  - addressing barriers in maintaining repositories of biological samples in resource-constrained countries;
  - developing and testing strategies for recruitment and retention of participants in prevention, treatment, and care studies;

- enhancing through IRBs the ability to ensure protection for human subjects involved in research and the ethical conduct of research, including informed consent and issues specific to women and children;
- enhancing mechanisms for information exchange among investigators, including enhanced electronic communication;
- conducting research on how to scale up from pilot projects and/or early Phase I and II trials to large research studies, including Phase III trials, and on how to apply research findings to the general population; and
- strengthening community advisory boards to participate in the development and design of clinical trials and other research, as well as in the translation of research results into programs and policies.

- Build global capacity to conduct operational research, including outcome and cost-effectiveness studies and modeling, to rapidly address emerging priorities in prevention, treatment, and care.
- Conduct studies on incidence and feasibility in order to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.
- Develop and provide training at international sites conducting vaccine studies on the role and responsibilities of an institutional biosafety committee (IBC).
- Develop regional approaches to research (e.g., through regional meetings and training) to enhance communication and to address common issues and needs among countries in a region.

Collaboration and Coordination

- Ensure that foreign investigators are full and equal partners to U.S. scientists in the design, conduct, and analyses of clinical studies.
- Enhance coordination of NIH international AIDS research, particularly when multiple projects are active in the same country and/or region.
- Encourage the continued development of research collaborations between international and U.S. investigators, ensuring project relevance to strategic planning at the local level, to maximize the research effort in resource-limited settings; and encourage U.S. researchers to participate at the developing country research site to better understand the challenges of conducting research and providing care and services in such settings.
- Provide assistance to foreign collaborators in addressing regulatory issues and special oversight mechanisms.

- Coordinate with other U.S. Government agencies, including the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and the State Department.
- Work with foreign governments, international organizations (e.g., WHO, with particular emphasis on coordinating research with WHO's 3x5 Program), GFATM, NGOs, private industry, and foundations to facilitate development and testing of vaccines, microbicides, drugs, and other prevention, care, and treatment strategies, including behavioral interventions.
- Explore collaborations with reputable indigenous health providers to better understand their roles and practices in HIV/AIDS care and prevention; to facilitate their involvement as partners and indigenous health professionals in global HIV/AIDS research, care, and prevention; and to identify practices that may add value in treating and preventing diseases in diverse geographical settings.

Ethical Issues

- Ensure that research projects are designed to benefit the countries in which the research is being conducted.
- Enhance the capability of institutions in resource-limited settings to conduct independent scientific and ethical reviews.
- Ensure education/cross-fertilization between resource-limited countries' ethical review committees and U.S. IRBs, and educate U.S. IRBs about cultural issues in developing countries.
- Ensure the participation of local researchers/scientists, communities, NGOs, and governments in the development of research protocols.
- Ensure that ethical challenges in both research and the implementation of research results in resource-limited settings are clearly described and addressed in grant proposals.
- Implement the *Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries*.
- Ensure confidentiality of information about HIV-infected individuals, including information on individuals in treatment for substance abuse.
- Ensure that ethical review mechanisms, such as informed consent forms, are relevant and appropriate to the country where the research is conducted and are placed in cultural context.

- Conduct workshops on ethical principles and their implementation in research, encouraging countries to develop their own set of ethical guidelines and procedures, to include the principles of respect for persons, beneficence, and justice, and the application of informed consent, assessment of risks and benefits, and selection of subjects.
- Encourage in-country scientists and leaders to work closely with local journalists to foster understanding of science, the role of research, and relevant ethical issues.
- Conduct research designed to identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings, including a focus on informed consent.

Technology Transfer and Translation of Research Results

- Ensure results are provided to participants and staff involved in research studies.
- Develop distance learning approaches to enhance communication of research results and translation into prevention, treatment, and care programs.
- Provide improved access to information concerning treatment and prevention guidelines and the results of research through enhanced information technology.
- Facilitate development of HIV prevention and treatment guidelines, adding behavioral, basic, and epidemiological aspects to clinical findings.
- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptom management, clinical training, and patient care programs once research studies are completed.

OBJECTIVE – B:

Develop a sustainable in-country scientific workforce by nurturing an environment that promotes a culture of local leadership and research on the part of in-country investigators, by mentoring of in-country investigators, and by providing opportunities for career development for junior scientists and scientists returning to their country following training.

STRATEGIES:

- Ensure the leadership role of in-country investigators and policy-level individuals in countries where studies take place by involving them in all stages of the research, including conceptualization of the research question, study design, development of protocols, study implementation and collection of data, data analysis, publication and presentation of research results, and interaction with the media.
- Develop in-country training partnerships, and support "south-to-south" training to enable investigators to obtain training appropriate for the areas in which they will work by (1) developing a cadre of in-country scientific professionals, and (2) providing opportunities to enable trained investigators returning to their home countries to serve as training resources for others.
- Continue to support training, both in-country and in the United States, of clinicians (physicians and nonphysician professionals, e.g., nurses, midwives, etc.), public health professionals, and scientists from developing nations to enhance the conduct of research on HIV, AIDS, sexually transmitted infections (STIs), and other HIV-related coinfections and malignancies, including research training related to (1) treatment and care, (2) clinical trials of therapeutic strategies for HIV and endemic coinfections, (3) development and testing of vaccine candidates, (4) impact of alcohol and other substance abuse/dependence on HIV transmission, (5) reproductive health, including microbicides, (6) disease progression, (7) prevention of MTCT, and (8) other biomedical, social, and behavioral prevention research.
- Provide training in data management and analysis for in-country research personnel.
- Provide training to enable in-country researchers to meet the requirements of GCP and GLP, including training and maintenance of medical records.
- Provide training in the ethical conduct of research, including informed consent and other topics related to the protection of human subjects.
- Provide training in all aspects of grantsmanship, including preparation of grant proposals, grants management, reporting requirements, research administration, and fiscal accounting.

- Provide training to ensure that clinicians and other health care workers are knowledgeable about infection control principles and can implement proper procedures in resource-constrained countries.
- Enhance training in translational and operational research.

OBJECTIVE – C:

Conduct studies to identify effective structural and policy interventions to address social conditions and to prevent concentrated epidemics from becoming generalized.

STRATEGIES:

- Develop better approaches to voluntary counseling and testing that encourage knowledge of one's status and help mitigate social harm, including changing community norms about acceptance of persons living with HIV/AIDS.
- Identify the most effective and sustainable ways to change or prevent high-risk sexual behaviors and practices (e.g., multiple partners, rape, trafficking of women and children into forced sex work and commercial sex work, and substance use and abuse) that foster the spread of HIV and other STIs.
- Investigate the effectiveness of community-based and community-level HIV prevention programs, including prevention education and strategies to evaluate, replicate, and extend effective behavioral interventions.
- Perform research on culturally appropriate content, form, and format of instruments that will improve the quality of culturally appropriate self-reports of sexual and drug use risk behaviors.
- Evaluate the effectiveness of expanded access to needle and syringe exchange programs.

OBJECTIVE – D:

Support research to develop interventions that address gender and gender relationships, as well as stigma and discrimination.

STRATEGIES:

- Conduct research on sex and gender differences in access and use of prevention and care services.
- Study gender-related social and behavioral factors affecting acquisition of HIV infection.
- Study gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as human papillomavirus (HPV) infection and cervical cancer.
- Study the psychological impact of HIV infection in women, including their role as heads of households and/or caregivers, the impact of additional pregnancies, and family support.
- Develop interventions to mitigate the negative social consequences of HIV infection related to AIDS stigma and discrimination, with particular emphasis on children infected with or affected by HIV (i.e., AIDS orphans).
- Evaluate strategies to reduce stigma and discrimination and increase willingness of individuals to enter into voluntary counseling and testing; identify, accept, and implement alternative infant feeding practices; and receive and adhere to ART regimens.

OBJECTIVE – E:

Study the significance of interactions between individuals among risk groups in order to develop effective control strategies, particularly as these interactions are manifest through the development of social networks (e.g., migration [and other cross-border issues] and displacement of people).

STRATEGIES:

- Develop sustainable behavioral and community-specific interventions to address multiple risk factors.
- Conduct research to integrate the multiple components of diverse issues of sexuality, alcohol and other substance use, and mental health into HIV prevention programs.
- Develop and test prevention strategies that address relationships between noninjection drug use and sexual transmission.
- Develop interventions targeted to both HIV-infected and HIV-uninfected individuals that are designed to appeal to specific populations such as women, men, adolescents, and the military.
- Develop and test prevention interventions to be used in the family context to prevent risky behavior and HIV acquisition and transmission by its members.
- Study the role of migration in the spread of the HIV epidemic in diverse geographical regions.
- Conduct studies to develop interventions at multiple levels (individual, couple, group, society) that reflect and address regional aspects of the epidemic.
- Investigate the role of alcohol and other commonly used psychoactive substances in promoting or facilitating high-risk sexual behaviors that reduce the efficacy of prevention strategies.
- Define sexual and drug use behaviors and their predictors in HIV-infected populations, and design and test interventions to reduce the risk of HIV transmission.
- Determine the factors involved in the social networks of injecting and noninjecting drug users and heavy drinkers that influence the rates and patterns of HIV infection, and design prevention programs based on these results.
- Study how alcohol use, including systems of payment using alcohol, affects increases in HIV risk in seasonal and nonseasonal migrant populations.

- Conduct studies to identify sustainable interventions at the levels of the individual, social network, community, and society to prevent HIV and HCV transmission as a result of high-risk sexual activity and/or drug use practices.
- Devise strategies to prevent initiation of drug use, alcohol dependence, and transition to riskier drug practices, such as initiating drug injection and sharing of injection equipment.

OBJECTIVE – F:

Develop and evaluate biomedical prevention interventions and strategies, including vaccines, microbicides, and other physical/chemical barriers; diagnosis and treatment of STIs; treatment of alcohol abuse and dependence and injecting drug use; and interventions to prevent MTCT.

STRATEGIES:

- Evaluate techniques for detection of acute HIV infection, and study the effects of early identification of potential HIV transmitters on HIV infection spread in different settings.
- Utilize population-based studies to examine basic scientific questions about HIV infection, mechanisms of transmission, and host responses, including viral evolution, viral diversity, human immunology, and mucosal factors in transmission.
- Study the risk of transmission of drug-resistant strains of HIV.

Vaccine Development

- Continue the accelerated efforts toward development of vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including candidates exhibiting low cost with ease of production and administration, as well as stability.
- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects.
- Provide a scientific knowledge base (incidence, viral subtypes, major histocompatibility [MHC] types, natural history) to guide decisionmaking regarding the need for clinical trials in international sites and to conduct trials in these sites and communities according to the highest clinical and ethical standards.
- Identify suitable populations of adults and children to enroll in clinical trials of candidate vaccines.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety, immunogenicity, and efficacy with suitable candidate vaccines in domestic and international settings.
- Enlist the participation of local community representatives in the development of appropriate trial protocols, as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively address the social and medical concerns of the participants; and establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.

- Examine relevant behavioral issues related to the conduct of vaccine research and its acceptability in diverse populations.
- Conduct research on the social and economic impact of vaccines and their cost-effectiveness.

Microbicides and Barriers

- Discover and develop candidate microbicides to prevent sexual transmission.
- Determine the efficacy and use of prevention interventions including microbicides and other physical/chemical barrier methods and determine the factors affecting their use.
- Determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.

STIs and Other Diseases

- Determine the efficacy and cost-effectiveness of syndromic management of STIs.
- Improve clinical management of viral STIs, emphasizing coinfections with herpes simplex virus (HSV)-2 and HPV.
- Identify gender-related biological factors affecting susceptibility to infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as HPV infection and cervical cancer.
- Examine the impact of coinfection with other endemic diseases on HIV disease, including the risk of acquiring and/or transmitting HIV infection and disease progression.
- Determine the role of sexual transmission of HCV in coinfection with HIV.

Substance Abuse

- Evaluate innovative, culturally relevant, contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings.
- Develop approaches for drug and alcohol abuse programs among HIV- and HCV-coinfected patients to improve adherence with drug/alcohol treatment strategies.
- Develop innovative strategies for identifying "hidden populations" of young drug users and out-of-treatment drug users.

MTCT: Considerations for the Mother, Infant, and Child

- Develop safe, effective, feasible, and conveniently administered strategies to interrupt MTCT, using interventions that are affordable and can be implemented in resource-constrained countries, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactation period.
- Develop and evaluate strategies for reducing the risk of MTCT, providing safe ART to pregnant women, and assessing the effects of variable length combination ART to HIV-infected women on both MTCT and the women's own health, including the impact on subsequent pregnancies.
- Study the effects of ARV regimens used for maternal health indications on the risk of MTCT (including postnatal transmission through breast milk) and other outcomes, including pregnancy outcomes.
- Investigate the mechanisms and timing of MTCT (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Further identify cost-effective, nondrug regimens for preventing MTCT, such as research on infant feeding, including:
  - acceptability of safe breastfeeding alternatives;
  - impact of the use of breast milk alternatives on morbidity and mortality of both the mother and infant; and
  - role of exclusive breastfeeding.
- Conduct studies to evaluate and reduce short- and long-term toxicities of ARVs in women during pregnancy and in their offspring who were perinatally exposed.
- Investigate the unique immune status of pregnant women and their infants and develop immune interventions to interrupt HIV transmission.
- Examine the role of maternal and infant nutrition during the peripartum and postpartum periods in reducing morbidity and mortality in HIV-infected mothers and their infants and in reducing MTCT.
- Study the impact of the health status of HIV-infected mothers on the survivability of both HIV-infected and HIV-uninfected children.
- Study the impact of breastfeeding on the health status of HIV-infected mothers.

OBJECTIVE – G:

Define the most effective strategies for treatment of HIV infection and its sequelae.

STRATEGIES:

- Determine affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment.
- Determine treatment efficacy, side effects, and toxicity of ARVs in adult, adolescent, and pediatric populations.
- Collaborate with clinicians from resource-constrained countries to recruit and retain acute and early HIV infection cases in treatment research programs.
- Determine the role of pharmacogenetics and identify appropriate ARVs that can be used in specific populations (e.g., adults, children, and adolescents) in resource-constrained countries.
- Determine the efficacy of ARV regimens on various clades prevalent around the world.
- Determine the pharmacokinetics of ARVs in various populations.
- Investigate interactions of ARVs with alcohol, drugs of abuse, or medications used for the treatment of substance abuse.
- Characterize the clinical course of HIV infection in diverse geographic settings.
- Identify conditions that emerge as a consequence of ART and longer survival, such as malignancies, neurological and neuropsychological conditions, and metabolic and nutritional dysfunctions.
- Support the long-term followup of children exposed to ART *in utero* and/or postpartum to evaluate possible late effects of ARV exposure.
- Assess the impact of nutritional status and nutritional interventions on patient survival and the efficacy and tolerability of ART, including measuring the rate of immune system deterioration.
- Develop and evaluate care models, such as family models of care, and enhance interdependent care services that integrate AIDS care into existing programs, such as TB control programs, alcohol and other substance abuse/dependence treatment programs, and maternal and child health services, to avoid duplication of efforts.

- Develop and evaluate strategies to initiate and provide care to targeted groups of individuals such as health care workers, security forces, and teachers.
- Conduct community-based studies that assess the impact of community mobilization on treatment success.
- Examine the effectiveness of a variety of approaches to the administration of therapy (e.g., directly observed therapy or directly delivered therapy).
- Conduct studies, including clinical trials and operational research, on the quality of treatment, its effectiveness, and its efficacy.
- Develop and test strategies to support adherence in adults and children to medication regimens to enhance therapeutic outcomes and limit the development of drug resistance.
- Investigate the impact of alcohol abuse, drug abuse, and other associated comorbid conditions on HIV disease progression, adherence to treatment regimens, and clinical outcomes.
- Develop and evaluate suitable, sustainable approaches for diagnosis of HIV infection, monitoring treatment safety and efficacy, side effects, and toxicities, with particular emphasis on finding affordable technologies to measure CD4+ cell counts and HIV load, as well as suitable alternatives.
- Assess the cost-effectiveness of ARVs in developing countries and determine the minimal level of ARV resistance monitoring necessary and the methods to be used for such monitoring.

OBJECTIVE – H:

Examine the interactions between HIV infection and endemic diseases, including the interactions in treatment of HIV infection in the context of preventing and treating malaria, tuberculosis, hepatitis, and STIs; and develop strategies to optimize diagnosis and treatment of coinfections and OIs, with a focus on studies that would not be conducted by the pharmaceutical industry.

STRATEGIES:

- Examine the role of coinfection with other endemic diseases and their treatment in modulating HIV infection or disease, including risk of acquiring and/or transmitting HIV infection and disease progression.
- Investigate the impact of coinfections with other endemic diseases and their treatment on the use of ART.
- Determine the impact of ART on susceptibility to infection with endemic diseases and on their natural history.
- Determine the impact of ART on the efficacy of treatment and prophylaxis for other endemic diseases.
- Investigate drug-drug interactions of ARVs and drugs used to prevent and treat endemic infections.
- Define the spectrum, incidence, and risk factors for HIV-related sequelae (e.g., coinfections such as TB, HCV, and HPV, malignancies, and organ system-specific manifestations such as renal disease, eye disease, urologic and neurological conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Determine optimal ways of integrating treatment for HIV and treatment for opportunistic infections and coinfections, especially TB, including clinical research to assess clinical outcome and operational research to determine cost-effectiveness.
- Investigate sustainable strategies for preventing, treating, and monitoring response to treatment of endemic coinfections.
- Assess the impact of available antibiotic treatment and prophylaxis regimens to optimize therapeutic approaches for TB and other endemic coinfections in the context of ART, including new therapies for TB and new approaches to administering drugs.
- Determine the safest and most efficient treatment modalities for endemic diseases (e.g., TB, HCV, and malaria) in the adult, pediatric, and adolescent populations infected with HIV.

- Develop methods to monitor development of antimicrobial resistance by HIV-related and endemic pathogens infecting both study participants and the general population.
- Develop strategies to enhance and monitor adherence to therapy/prophylaxis for endemic coinfections.
- Determine the safety and effectiveness of available immunizations for endemic pathogens in diverse HIV-infected populations.
- Develop simple clinical algorithms for guiding initiation of prevention or treatment of HIV-related coinfections and opportunistic infections.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in HIV-coinfected individuals in various settings.
- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related coinfections and OIs.
- Conduct studies to better understand the role and mechanism of reinfection and/or superinfection with HCV in coinfected individuals.

OBJECTIVE – I:

Evaluate the impact of treatment on the HIV epidemic, taking advantage of HIV treatment "rollout programs."

STRATEGIES:

- Assess the impact of ART on risk behaviors, HIV transmission and prevalence, including associated behavior change, in various communities.
- Determine the social, psychological, societal, and economic impact of ART on individuals (including children), families, and communities, including the impact on personal risk behaviors.
- Determine the impact of ART availability on utilization of voluntary counseling and testing (VCT) in various communities.
- Determine the impact of ART availability on entry into care and treatment.
- Determine whether expanded ART care and treatment leads to a decrease in HIV-associated stigma and discrimination.
- Evaluate the impact of interactions between HIV therapeutics, alcohol, drug abuse, or medications used for the treatment of substance abuse on the maintenance of antiaddiction therapy and on MTCT.
- Determine the impact of ART on breastfeeding behaviors.
- Study the direct effects of ART on HIV transmission, e.g., by evaluating the effectiveness of specific ART strategies in curtailing HIV transmission in HIV-discordant couples.
- Determine the public health impact of ART, specifically the likelihood of transmission of drug-resistant virus and the natural history of disease in people infected with a drug-resistant HIV strain.
- Determine the impact of ART on the development of drug-resistant strains of HIV in diverse geographical settings, and develop strategies to limit its development.
- Develop biomarkers that can serve as surrogates for measurement of HIV risk behavior and can be used to predict and monitor rapid escalation of HIV subepidemics.
- Support operational research to facilitate the translation of research findings to clinical practice and public health programs and to provide information to inform the scaleup of treatment programs.

OBJECTIVE – J:

Conduct studies to develop strategies to optimize the synergy between prevention and treatment.

STRATEGIES:

- Conduct studies to determine effective strategies for integrating the delivery of HIV care with drug treatment, alcohol treatment, TB treatment, and other medical and social services commonly needed by HIV-infected individuals.
- Develop strategies to ensure that prevention efforts in resource-limited countries are simultaneously preserved and enhanced when treatment clinical trials and, later, ART treatment programs are established.
- Encourage research on integrating prevention and care services.
- Conduct research on how best to deliver prevention education in the care and treatment setting, targeting interventions to both HIV-uninfected and -infected individuals.
- Integrate operational and health services research with clinical research to facilitate the translation of research findings into clinical practice and public health programs, addressing HIV disease in the context of other diseases, access to health care, and prevention programs.
- Examine the potential use of HIV therapeutic vaccines.
- Develop culturally appropriate mechanisms to identify persons for whom treatment is indicated, and to overcome factors such as stigma and discrimination, which can forestall testing and limit the provision of treatment and care.
- Determine barriers and facilitators to acceptance of voluntary HIV counseling and testing and treatment and/or prevention programs.
- Conduct studies to develop new approaches to voluntary counseling and testing and assess them for cost-effectiveness and impact on reducing risk from sexual behavior and drug use in settings with varying levels of HIV seroprevalence.
- Conduct multidisciplinary prevention research in multiple settings, including medical treatment and community support and care organizations.
- Develop links with other agencies and organizations to integrate research with service programs and to develop multidisciplinary collaborations.
- Conduct translational and operational research to accomplish widespread delivery of interventions to prevent transmission of HIV infection and to provide care and treatment for those individuals and families affected by HIV.
- Conduct research on how to scale up from research studies to implementation of prevention and care programs.

FY 2007 OAR Planning Group for International Research

FY 2007 INTERNATIONAL RESEARCH PLANNING GROUP

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